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Perceived Visual Distortions in Juvenile Amblyopes During/Following Routine Amblyopia Treatment

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Purpose. To establish the point prevalence of perceived visual distortions (PVDs) in amblyopic children; the association between severity of PVDs and clinical parameters of amblyopia; and the relationship between PVDs and amblyopia treatment outcomes.

Methods. Perceived visual distortions were measured using a 16-point dichoptic alignment paradigm in 148 visually normal children (aged, 9.18 ± 2.51 years), and 82 amblyopic children (aged, 6.33 ± 1.48 years) receiving or following amblyopia treatment. Global distortion (GD; vector sum of mean-centered individual alignment error between physical and perceived target location) and Global uncertainty (GU; SD of GD over two experiment runs) were compared to age-matched control data, and correlated against clinical parameters of amblyopia (type, monocular visual acuity, pretreatment interocular acuity difference, refractive error, age at diagnosis, motor fusion, stereopsis, near angle of deviation) and amblyopia treatment outcomes (refractive adaption duration, treatment duration, occlusion dosage, posttreatment interocular acuity difference, number of lines improvement).

Results. Point prevalence of PVDs in amblyopes was 56.1%. Strabismic amblyopes experienced more severe distortions than anisometropic or microtropic amblyopes (GD Kruskal Wallis H = 16.89, $P < 0.001$; GU Kruskal Wallis H = 15.31, $P < 0.001$). Perceived visual distortions severity moderately correlated with the strength of binocular function, (e.g., log stereoacuity [GD rho = 0.419, $P < 0.001$; GU rho = 0.384, $P < 0.001$)], and strongly with near angle of deviation (GD rho = 0.578, $P < 0.001$; GU rho = 0.384, $P < 0.001$). There was no relationship between severity of PVDs and amblyopia treatment outcomes, or the amblyopic visual acuity deficit. Perceived visual distortions persisted in more than one-half of treated amblyopic cases whose treatment was deemed successful.

Conclusions. Perceived visual distortions are common symptoms of amblyopia and are correlated with binocular (stereoacuity, angle of deviation), but not monocular (visual acuity) clinical outcomes. This adds to evidence demonstrating the role of decorrelated binocular single vision in many aspects of amblyopia, and emphasizes the importance of restoring and improving binocular single vision in amblyopic individuals.

Keywords: amblyopia, binocular vision, strabismus, psychophysics

Our group recently modified and piloted a binocular paradigm for mapping perceptual visual distortions (PVDs) in amblyopia for a group of 24 amblyopic individuals and 10 control participants (mean age 27.13 ± 10.20 years).[1] We reported that visual distortion remained consistent over time and correlated to strength of binocular single vision, size of the angle of ocular deviation, and (marginally) amblyopic eye visual acuity (VA). However, the former two variables were strongly correlated with each other, making it difficult to determine their respective contributions to the severity of PVD experienced. Having validated the paradigm, it can now be applied to the task of evaluating the occurrence of PVDs in children and exploring these relationships to other clinical endpoints.

The sample size for previous studies evaluating PVDs in children with amblyopia[2–4] is somewhat limited. One study[3] utilized a cohort of 32 children with strabismic, mixed, and microtropic amblyopia, of whom 14 participants had displacement and uncertainty, while 6 had uncertainty only. This yields a point prevalence of 62.5% for PVDs in that sample, slightly below the prevalence that has been reported for adult amblyopes (between 67%[5] and 71%,[6] although assessment methods varied between studies). Our cross-sectional study in a larger sample of children will provide a more representative point prevalence.

In our previous study, all except two of our sample of adult amblyopes with significant PVDs had received amblyopia treatment as children, a finding supported by many other studies.[5–14] We also identified a marginally significant relationship between amblyopic eye acuity and distortion severity. These results are consistent with the hypothesis that unsuccessful or partially successful amblyopia treatment (cases in which acuity in the amblyopic eye remains reduced) could be associated with more severe distortions. According to this hypothesis, patients without distortion may be more likely to have successful treatment outcomes, and therefore drop out of the amblyopic population. Fronius et al.[4,15] identified improvements in the severity of PVDs for juvenile amblyopes during the

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Table 1. Inclusion Criteria for the Two Study Arms

Visually Normal Control Children (Glasgow Science Centre)	Amblyopic Children (Gartnavel General Hospital)
Age 5–18 y	
No developmental disorder such as Down's Syndrome or autism	
Ability to complete all 3 runs of the dichoptic task	
No history of amblyopia/strabismus	Receiving or have received amblyopia treatment
VA in each eye of 0.100 logMAR or better	No other pathology contributing to reduced VA (e.g., nystagmus, retinal disease)
IOAD < 0.100 logMAR	IOAD > 0.100 logMAR at the start of amblyopia treatment
Well-controlled heterophoria < 10Δ on cover test	No DVD
Stereoacuity of 60" arc or better on TNO stereotesting	

course of occlusion therapy, but the extent of improvement and relationship to the VA change is unclear. There is, therefore, a possibility that the existence of severe PVDs may influence amblyopia treatment outcomes, or vice versa.

If severity of PVDs were to interact with amblyopia treatment outcomes, one would expect individuals with more severe PVDs to have a greater degree of residual amblyopia, longer treatment durations, and higher doses of occlusion, due to a sluggish treatment response. A cross-sectional study of children with amblyopia who have completed conventional treatment could identify such trends, through retrospective access to detailed treatment information. This addresses difficulties experienced by Fronius et al.,[3] who discussed in their paper the struggle to obtain precise clinical histories of children they tested.

Fronius et al.[3] found a significant interaction between age and measured PVD in their control children, emphasizing the importance of age-matching amblyopic and control participants. Accordingly, the current study will also enable comparison of the clinical parameters of children who do have significant PVDs against those who do not, to identify clinical parameters that differ between the two groups and potentially determine the predicting factors for whether a child will or will not experience PVDs.

The overall aims of this study are therefore:

1. To establish the point prevalence of PVDs in a large sample of amblyopic children;
2. To ascertain the relationship between severity of PVDs and clinical parameters of amblyopia; and
3. To determine whether more severe PVDs are associated with poorer amblyopia treatment outcomes.

Methods

Participants

One hundred forty-eight visually normal control children (aged 9.18 ± 2.51 years), and 82 amblyopic children (aged 6.33 ± 1.48 years) were recruited from two sites (Glasgow Science Centre for the control children [Glasgow, Scotland], Gartnavel General Hospital for the amblyopic children [Glasgow, Scotland]). Inclusion criteria are shown in Table 1. Amblyopes with dissociated vertical deviation (DVD) were excluded, as this clinical entity is characterized by a large, variable vertical deviation in association with dense suppression, independent of the strabismus that it overlays.

In accordance with local treatment protocols at the treatment site, amblyopia was defined as the presence of a consistent interocular acuity difference (IOAD) greater than 0.100 logMAR. Anisometropia was defined as an interocular refractive error difference of greater than 1.00 dioptric sphere or greater than 1.00 dioptric cylinder.[16–18]

Procedure

Recruitment. Visually normal control children were recruited from the general public attending Glasgow Science Centre in July 2013. This study arm was approved by Glasgow Caledonian University (Glasgow, Scotland) Research Ethics Committee. Informed consent was not required because all data collected was anonymous, with only the child's age and first letter of their first name being recorded. However, parents were provided with an information sheet that explained the study, and had the option to request that their child's data not be used, in which case it was deleted.

Amblyopic children were recruited from outpatient attendances at Gartnavel General Hospital Orthoptic Department. Information sheets were provided for parents prior to testing, informed consent was taken from the parent/guardian, and assent obtained from children aged 7 years and older. This study arm was approved by West of Scotland Research Ethics Committee. Both study arms followed the tenets of the Declaration of Helsinki.

Measurement of PVDs. In both arms, children completed a child-friendly version of the dichoptic distortion mapping task used previously[1] (Fig. 1), to measure their global distortion (GD) and global uncertainty (GU). All stimuli were presented using MATLAB 2012b (Mathworks, Natick, MA, USA) running PsychToolbox 3.0 on Windows 7 (Redmond, WA, USA). Viewing distance was 50 cm. Participants viewed a central fixation dot (0.41°), which changed to a random color with experimenter keypress. The child was instructed to state the color whenever it altered, in order to ensure fixation compliance. Any child who failed to give correct responses was excluded ($n = 10$).

To the left eye a mouse cursor was presented in a crosshair shape (arms 1.09° × 0.10° with 3.26°-gap centrally to minimize binocular rivalry against the target stimulus). To the right eye, a target stimulus (0.41°-diameter circle) was presented at one of 16 target locations forming two nested rectangles covering the central 2.5° of the visual field. Children were instructed to use a computer mouse to move the crosshair onscreen, in order to frame the target with the crosshair and click on it. Upon clicking the mouse, mouse x and y pixel coordinates relative to the top left corner of the screen were recorded. The target dot then moved to another of the 16 locations in random order. The mouse was set up for right-handed use but could be changed to be on the left-hand side of the computer at the child's request. However, no child requested to use the mouse left-handed. The task was designed with three 'levels' to encourage children to play it again (Fig. 1), allowing performance of three repeats within a single session. The task was identical between 'levels' with only the pictures at the top of the screen changing (their dimensions remained the same). All task-essential stimuli were unchanged. There was no time limit for task completion.

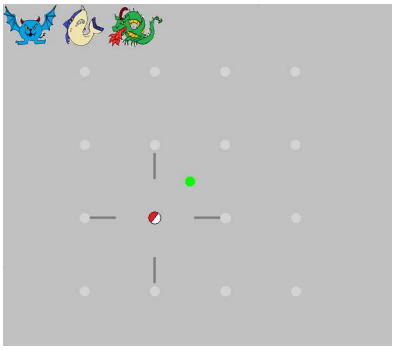

Figure 1. Child-friendly adaptations of the dichoptic mapping task. Monster Evolution - Collected cartoon characters were displayed at the top of the screen (note characters displayed are placeholder graphics and not to scale). The *gray 12-pixel target dot* has been replaced by a *red and white ball* of the same diameter. The *green central fixation dot* changed color with a keypress.

Clinical Testing. At Glasgow Science Centre, children underwent a basic vision screening test consisting of a uniocular visual acuity measurement of both eyes using Keeler crowded LogMAR books (Keeler, Windsor, UK) at 3 m, a cover test to identify heterophoria size and control, and a TNO stereotest (TNO, Nieuwegein, The Netherlands). If the child failed the screening test, their parents were informed of the outcome and advised to see their local optometrist.

At Gartnavel General Hospital, clinical data (see Table 2 for list) was obtained from the child's case notes after informed consent was taken. A diagnosis of microtropia was only made if confirmed by presence of a suppression scotoma on 4Δ prism reflex testing or eccentric fixation in the absence of manifest strabismus on visuoscopy. In Fronius et al.,[3] no differentiation was made between microtropia and other types of strabismus in their sample, despite microtropia being a rather different clinical entity to that of, for example, partially accommodative esotropia.

Statistical Analysis

For all participants, the first run of the experiment was discarded as a practice, thus two runs were analyzed for each participant. Heterophoric/heterotropic angle of deviation was accounted for within the PVD measurement by calculating the mean horizontal and vertical local displacement value for each of the 16 points across both runs of the experiment, and subtracting this value from their results prior to analysis. Global distortion was then defined as the vector sum of individual alignment error between the physical and perceived locations of the targets. Global uncertainty was defined as the SD of the GD over the two experiment runs.

Glasgow Science Centre Arm. For data obtained from this study arm, a jack-knifing normalization procedure[19] was used. Jack-knife estimation was performed by calculating the mean of a dataset repeatedly, systematically leaving out one sample in the dataset each time the calculation is performed and creating jack-knife estimates. By subtracting the mean of these estimates from each individual jack-knife estimate, a jack-knife distance (the distance from the jack-knife estimate to the mean) can be calculated. Having calculated these jack-knife distances, of which there will be one for each data point (16 data points in each run of the dichoptic mapping task—one for each target location), any jack-knife distance that exceeds 1.96 × SD of the jack-knife mean can be classed as an outlier and the associated data point excluded.[19] This jack-knifing procedure was performed in MATLAB (Mathworks), and data points associated with abnormal jack-knife distances were excluded by replacing them with NaN (not-a-number) values, which can be accounted for during analysis by the use of the nanmean() and nanstd() functions in MATLAB.

Table 2. Clinical Data Obtained During the Gartnavel General Hospital Arm of the Study

Clinical Data Type
Stage of treatment (during/completed)
Current age
Diagnosis
Treatment received (glasses, occlusion, atropine, surgery)
Treatment compliance (good, fair, poor)
Age at diagnosis
Refractive adaptation length (length of time child wore glasses alone before starting amblyopia treatment)
Treatment duration
Occlusion/atropine dosage
Current refractive prescription (in diopter-sphere and diopter-cylinder)
Current VA (in logMAR)
Current IOAD (in logMAR)
IOAD at start of treatment (in logMAR)
Number of lines improvement in VA with treatment (in logMAR)
Current cover test findings
Sensory fusion status (normal/abnormal as determined by 4Δ prism test or visuoscopy, absent as determined by negative Bagolini glasses response for near and distance)
Most recent near (33 cm)-horizontal prism fusion range results (in prism diopters, base in and base out)
Most recent stereotest result (in arc s; most commonly Frisby stereotest but occasionally the TNO test was used)
Most recent near (33 cm)-prism cover test result (in prism diopters)

Following jack-knifing, PVD data was found to be normally distributed, therefore parametric statistics were performed using SPSS 20 (IBM, San Jose, CA, USA). Bonferroni-corrected *t*-tests compared GD and GU between consecutive and preceding ages (e.g., values from children aged 6 were compared with children aged 5 and 7 years). Ages between which there were no significant differences in GD or GU were merged to form an age bracket, with the *t*-test repeated for the newly formed age brackets. Creating age brackets in this way improves statistical power in comparison to comparing each amblyope to a control group of their specific age. Global distortion and GU indices were also Pearson-correlated against age to identify any associations between age and these measurements.

Gartnavel General Hospital Arm. Some amblyopic children ($n = 6$) accidentally clicked the central fixation target on color change, or lost the mouse cursor and clicked off screen—these data points within runs were manually excluded and replaced with NaN in MATLAB, prior to post processing as documented previously.[1] Many clinical parameters (motor fusion, stereoacuity, near-prism cover test) were interval in nature and highly skewed due to floor effects, thus nonparametric statistics were used with this group. Stereoacuity values underwent logarithmic conversion for analysis. Children with stereoacuity not measurable by any clinical test had a stereoacuity value of 4.00 log arc seconds assigned for analysis purposes.

Distortions were identified in amblyopic individuals by examining each participant's mean GD and GU. If either of these values exceeded the 95% confidence interval (CI) for control participants in their age bracket, with brackets determined during the analysis of the normative data, they

Table 3. Normative Values for GD and GU, by Age

Age (y)	Dichoptic PVD (Mean of 3 Repeats ± SD)	Dichoptic PVD (Mean of Age Bracket ± SD)
5 ($n = 11$)	GDI (°) 0.54 ± 0.15	GDI (°) 0.50 ± 0.13
	GUI (°) 0.29 ± 0.10	GUI (°) 0.26 ± 0.08
6 ($n = 16$)	GDI (°) 0.50 ± 0.14	
	GUI (°) 0.26 ± 0.09	
7 ($n = 16$)	GDI (°) 0.48 ± 0.12	
	GUI (°) 0.24 ± 0.06	
8 ($n = 13$)	GDI (°) 0.40 ± 0.09	GDI (°) 0.42 ± 0.09
	GUI (°) 0.19 ± 0.04	GUI (°) 0.21 ± 0.06
9 ($n = 16$)	GDI (°) 0.42 ± 0.11	
	GUI (°) 0.21 ± 0.06	
10 ($n = 22$)	GDI (°) 0.44 ± 0.08	
	GUI (°) 0.22 ± 0.06	
11 ($n = 18$)	GDI (°) 0.37 ± 0.12	GDI (°) 0.38 ± 0.11
	GUI (°) 0.20 ± 0.06	GUI (°) 0.20 ± 0.07
12 ($n = 13$)	GDI (°) 0.36 ± 0.10	
	GUI (°) 0.20 ± 0.08	
13 ($n = 11$)	GDI (°) 0.41 ± 0.12	
	GUI (°) 0.20 ± 0.06	
14 ($n = 4$)	GDI (°) 0.43 ± 0.14	
	GUI (°) 0.23 ± 0.11	

Middle column shows normative values for each age, right-most column shows normative values for age-brackets determined by *t*-testing.

were classified as having significant PVDs that could not be attributed to mouse-click error alone.

To identify any relationship between clinical parameters of amblyopia and severity of PVDs, GD and GU were correlated against age at diagnosis, length of refractive adaptation, IOAD at start of treatment, current VA in each eye, binocular single vision parameters (motor fusion break amplitudes and stereoacuity), and the near angle of deviation (near-prism cover test). This correlation was performed for the whole group, irrespective of whether or not they had significant PVDs, as such relationships would be expected to hold regardless of whether the PVD were outside normal limits. In addition, to identify which clinical parameters are associated with the presence or absence of significant PVDs, a Mann-Whitney *U* test was performed comparing current age and the above-listed clinical parameters between amblyopes with significant PVDs and amblyopes without.

Further exploration of this was carried out by performing a multiple linear regression analysis of GD and GU against age and the clinical parameters of stereoacuity, motor fusion (base in and base out), and the near angle of deviation, as these variables were found to be significantly correlated. Global distortion and GU were both reciprocal transformed following scatter plot analysis to reduce hetereoscedascity. An initial regression was performed using all variables entered for the purposes of outlier analysis, as the skewed nature of the independent variables under analysis increases the impact of outliers on the result of the regression. Two data points creating residuals greater than 2 or less than −2 were subsequently removed from analysis for GU, and a further three for GD. The multiple regression analysis was then repeated following outlier analysis ($n = 80$ for GU, $n = 77$ for GD), with stepwise approach based on *F* probability removal for the independent variables.

To assess the impact of amblyopia type on severity of PVDs, a Kruskal-Wallis test was performed on those amblyopic children who had significant PVDs ($n = 46$), with individual, Bonferroni-corrected Mann-Whitney *U* tests performed if a significant difference was identified.

To evaluate the impact of PVD severity on treatment outcomes, individuals who had completed treatment ($n = 52$) were analyzed. Treatment duration, current IOAD, number of lines improvement, motor fusion, stereoacuity, and near-prism cover test results were correlated against severity of GD and GU measures. In addition, a Mann-Whitney *U* test was also performed to compare amblyopes with significant GD and/or GU against amblyopes without to determine whether differences in clinical parameters between these two groups exist following amblyopia treatment.

Results

Glasgow Science Centre Arm

One hundred forty-eight participants were recruited. Presented here is the data for participants aged 5 to 14 years ($n = 140$), as only seven participants older than 14 years were recruited and the oldest amblyope was aged 14. Table 1 shows mean PVDs by age and age bracket. A statistically significant difference was found between children aged 7 and those aged 8 for GU ($t = 2.48$, df = 27, $P = 0.020$), and between children aged 10 and those aged 11 for GD ($t = 2.48$, df = 38, $P = 0.018$). Thus, visually normal participants were bracketed into ages 5 to 7, 8 to 10, and 11 to 14 (Table 3). This table indicates reducing GD and GU between ascending age brackets, although some variation exists within brackets. Figure 2A shows a scatter plot of GD against age, while Figure 2B shows the relationship for GU, with trend lines demonstrating a reduction in these parameters with increasing age. This is supported by weak, negative correlations of GD (Pearson's $R = -0.347$, $P < 0.001$) and GU (Pearson's rho = −0.300, $P < 0.001$) against age. These findings justify the use of an age-matched control group for comparisons with the amblyopic children, and emphasize the need to account for age in any regression analyses performed.

Estimation of Sample Size for Recruitment of Amblyopic Children. Using GD data for visually normal children aged 5 to 7 years (as it was the largest), an effect size was calculated using G*Power 3[20] to detect a difference in GD of 1.96 × SD of the GD measurement for that age bracket. The difference to be detected was 0.26°, yielding an effect size of 0.89. G*Power 3 recommended a sample size of 35 amblyopes using Mann-Whitney *U* test with a minimum asymptotic relative efficiency distribution. Based on the point prevalence information from Fronius et al.,[3] a 62.5% prevalence rate of PVDs would require the sample size to be revised up to 56 amblyopes. However, as the sample size for that study was relatively small ($n = 32$), recruitment was performed as if the prevalence rate were lower (50%), with a 10% safety margin, yielding an estimated sample size of 77 amblyopes to recruit.

Gartnavel General Hospital Arm

Eighty-two amblyopic children were recruited (29 strabismic/mixed, 13 anisometropic, 40 microtropic). Of these, 52 (63.4%) had completed amblyopia treatment at the time of testing. Forty-six participants had significant PVDs (GD and/or GU) exceeding the 95% CI of the control participants for their age bracket, yielding a point prevalence of 56.1%. Clinical parameters for all 82 amblyopic participants, separated into those who have significant PVDs and those who do not, are shown in Table 4. Table 5 compares GD and GU for the control participants against those of the amblyopic participants with significant PVDs, by age bracket.

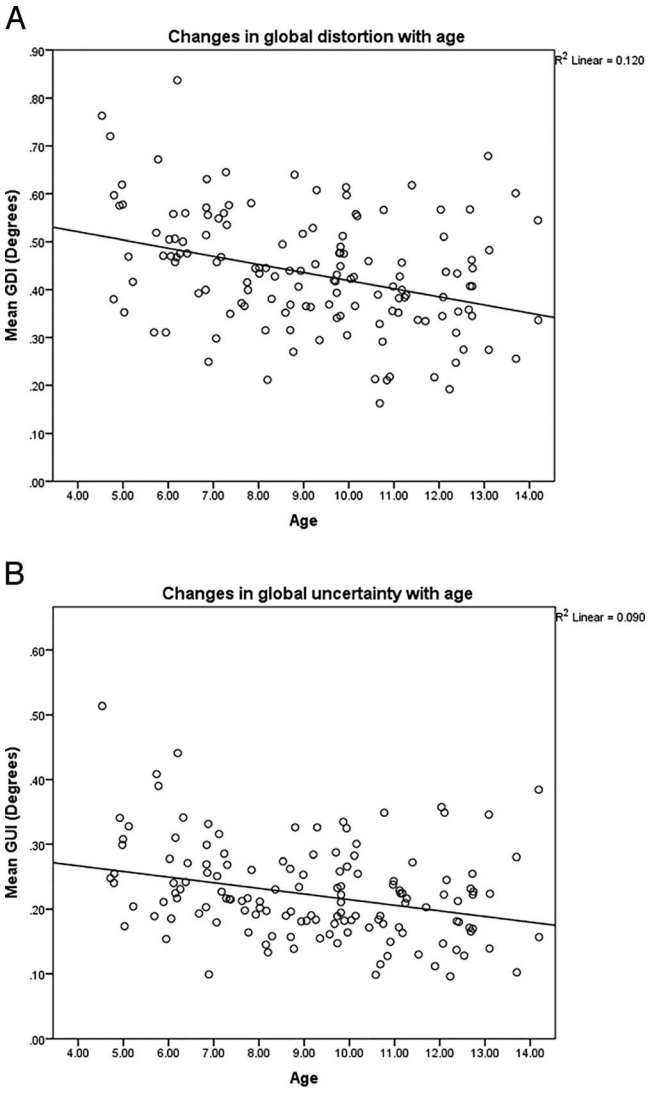

FIGURE 2. Changes in the GD index (**A**) and GU index (**B**) with age in individual visually normal children. The index measure decreases with increasing age.

Amblyopes with significant PVDs had a younger age of diagnosis, poorer VA (although this was only statistically significant for the fellow eye), poorer binocular function (median unmeasurable stereoacuity and absent prism fusion reserves), and a larger near angle of deviation. They also had a longer refractive adaptation period, although this was not statistically significant. Initial amblyopia density (pretreatment IOAD), and current amblyopia density (the current IOAD) were not significantly different between the two groups.

These differences were supported by whole-group correlation analysis (Table 6). Moderate negative correlations were identified between GD/GU indices and age at diagnosis, as well as motor fusion base in and base outbreak amplitudes. Thus, GD/GU indices appear to increase with reducing fusional amplitudes or a younger age at diagnosis.

Table 6 shows statistically significant results for the correlational analysis. Weak to moderate positive correlations were also identified with GD/GU for log stereoacuity and near angle of deviation. A larger log stereoacuity value indicates poorer stereoacuity, thus severity of the PVDs measured increases with deteriorating stereopsis and increasing angle of deviation. Weaker positive correlations were also identified between GD/GU and VA in the fellow eye. Global uncertainty was also found to be weakly correlated with age at time of testing.

The Contribution to GD/GU Made by Strength of Binocular Function and the Near Angle of Deviation. Binocular functions (motor fusion and stereoacuity) strongly correlated to the near angle of deviation (motor fusion base in break amplitude rho = –0.703, $P < 0.001$; base outbreak amplitude rho = –0.743, $P < 0.001$; stereoacuity rho = –0.699, $P < 0.001$). This correlation makes it difficult to isolate strength of binocular functions from the near angle of deviation as factors in PVD severity, as discussed previously.[1] However, the larger sample of amblyopic children tested in this study enables some exploration of this relationship via multiple linear regression.

For GU ($n = 80$), significant contributors (adjusted $R^2 = 0.329$, $F(3, 76) = 13.91$, $P < 0.001$) were near angle of deviation, motor fusion base in break amplitude, and marginally, age. For GD ($n = 77$), the only significant contributor

TABLE 4. Differences in Clinical Parameters Between Amblyopes With Significant PVDs ($n = 46$) and Those Without ($n = 36$)

Clinical Parameter	Amblyopes With Significant PVDs ($n = 46$)	Amblyopes Without Significant PVDs ($n = 36$)
Age at diagnosis (y), mean ± SD	3.30 ± 1.19*	4.25 ± 1.63
Current VA (logMAR), mean ± SD		
Amblyopic eye	0.33 ± 0.21	0.24 ± 0.14
Fellow eye	0.08 ± 0.09*	0.02 ± 0.08
Current MSE prescription (DS), mean ± SD		
Amblyopic eye	+5.01 ± 2.23	+4.54 ± 3.04
Fellow eye	+4.08 ± 2.35	+3.26 ± 2.07
Refractive adaptation (mo), mean ± SD	11.00 ± 9.34	8.72 ± 8.20
Pretreatment IOAD (logMAR), mean ± SD	0.42 ± 0.24	0.42 ± 0.23
Current IOAD (logMAR), mean ± SD	0.24 ± 0.22	0.23 ± 0.14
Horizontal prism fusion range (Δ), median (IQR)		
Base in	0 (12.00)*	15.00 (12.00)
Base out	0.50 (26.25)*	32.50 (25.50)
Stereoacuity (" arc), median (IQR)	Unmeasurable (91)*	160 (59)
Near angle of deviation (Δ), median (IQR)	11.00 (14.00)*	5.50 (8.75)

Participants with no measurable stereopsis were assigned a log arc second value of 4.00.
* Significantly different to amblyopes without PVD (Mann-Whitney U test, $P < 0.05$).

Table 5. Comparison of GD and GU Between Control Participants and Amblyopic Participants With Significant PVDs

Age, y	Control Dichoptic PVD, Mean of Age Bracket ± SD	Amblyopic Dichoptic PVD, Mean of Age Bracket ± SD
5–7		
Control $n = 43$	GDI (°) 0.50 ± 0.13	GDI (°) 1.25 ± 0.59
Amblyopic $n = 37$	GUI (°) 0.26 ± 0.08	GUI (°) 0.87 ± 0.41
8–10		
Control $n = 51$	GDI (°) 0.42 ± 0.09	GDI (°) 0.68 ± 0.25
Amblyopic $n = 9$	GUI (°) 0.21 ± 0.06	GUI (°) 0.44 ± 0.22
11–14		
Control $n = 46$	GDI (°) 0.38 ± 0.11	N/A
Amblyopic $n = 0$	GUI (°) 0.20 ± 0.07	

(adjusted $R^2 = 0.401$, $F(1, 75) = 51.80$, $P < 0.001$) was near angle of deviation. Table 6 shows the regression coefficients and P values for these variables. There was no significant contribution made by stereoacuity or base out motor fusion break amplitudes to prediction of GD or GU.

As the dependent variable for regression was the reciprocal of GD or GU, these findings indicate that when the other variables are held constant, PVDs increase with increasing angle of deviation, and GU decreases with increasing base in fusional amplitudes or age. Thus, values of GD or GU for each 1-unit change in a given variable ($\hat{y}$) can be partially predicted using the following equation, where y is current GD or GU in degrees and c is the unstandardized beta regression coefficient as drawn from Table 7:

$$\hat{y} = \frac{1}{\frac{1}{y} + c} \quad (1)$$

As an example, a participant with 0.98° of GU would experience a predicted 0.05° increase for every prism diopter increase in the near angle of deviation and 0.04° increase for every prism diopter decrease in base in motor fusion break amplitude. Age would temper this change by a predicted 0.15°.

Effect of Amblyopia Type Upon PVDs. Severity of PVDs was affected by amblyopia type (GD Kruskal Wallis H = 16.89, $p < 0.001$; GU Kruskal Wallis H = 15.31, $P < 0.001$). Figure 3 shows mean GD and GU indices by amblyopia type. Strabismic amblyopes have more GD and uncertainty compared with anisometropic and microtropic amblyopes, confirmed by Mann-Whitney U testing (strabismic versus microtropic, GD $Z = -3.76$, $P < 0.001$, GU $Z = -3.67$, $P < 0.001$; strabismic versus anisometropic, GD $Z = -3.12$, $P = 0.001$, GU $Z = -2.71$, $P = 0.006$). There was no significant difference in GD or GU indices between microtropic and anisometropic amblyopes (GD $Z = 0$, $P = 1$, GU $Z = -0.62$, $P = 0.54$).

Impact of PVDs on Amblyopia Treatment Outcomes. Treatment outcomes for those who had completed treatment ($n = 52$), along with VA, refractive error, binocular functions, and the near angle of deviation, are shown in Table 8, separated by presence/absence of PVDs. Mann-Whitney U testing between the two groups shows little difference in findings from that of the whole sample. There was no significant difference in treatment outcome variables (treatment duration, occlusion dose, initial IOAD, posttreatment IOAD, number of lines improvement) between amblyopes with and without PVDs, after amblyopia treatment conclusion. Similarly, correlational analyses found no significant relationship between the above treatment outcome variables and PVD severity. Overall, there were no associations that could be identified between poor treatment outcomes and presence/severity of PVDs.

Discussion

Prevalence of PVDs

The point prevalence of binocular PVDs in this population was found to be 56.1%. This estimate is slightly lower than that found for monocular PVDs by Fronius et al.[3] (62.5%), and in adult amblyopes (67%[5]–71%[6]). The current study has recruited the largest sample of any known study into PVDs in amblyopic individuals, and included anisometropic and microtropic amblyopes in addition to strabismic. Our study used age-bracketed 95% CIs of GD/GU values from the control children as an upper limit criterion for determining presence of significant GD/GU in the amblyopic children. This may have led to the above quoted figure being an underestimate of prevalence of PVDs in this group. However, we would rather our figure stood as a minimum prevalence than have the possibility that some of the children be classified as having PVDs when their GD and GU values could have been attributed to mouse-click error alone.

Impact of Amblyopia Type Upon Severity of PVDs

Strabismic amblyopes were found to have greater distortion than microtropic and anisometropic amblyopes (Fig. 4), and may therefore explain the differences in estimates of prevalence between our study and previous estimates. Separation of microtropic amblyopes from strabismic amblyopes during analysis is a unique approach not performed in other studies. Previous studies including microtropic and strabismic amblyopes in the same sample for analysis on the basis of both possessing a heterotropia,[6,12,21] may have potentially had stronger findings had they considered the microtropic amblyopes separately.

Table 6. Significant Correlations Between PVDs and Clinical Parameters of Amblyopia ($n = 82$)

Clinical Parameter	Global Distortion, Rho (P Value)	Global Uncertainty, Rho (P Value)
Age	Not significant	−0.246 (0.026)
Fellow eye VA	0.300 (0.006)	0.267 (0.015)
Age at diagnosis	−0.502 (<0.001)	−0.422 (<0.001)
Motor fusion break amplitude		
Base in	−0.435 (<0.001)	−0.502 (<0.001)
Base out	−0.449 (<0.001)	−0.455 (<0.001)
Log stereoacuity	0.419 (<0.001)	0.384 (<0.001)
Near angle of deviation	0.578 (<0.001)	0.384 (0.001)

TABLE 7. Regression Coefficients, Significance, and Collinearity for Statistically Significant Independent Variables Within the Multiple Linear Regression Analysis

Variable	Regression Coefficients		*P* Value	Variance Inflation Factor
	Unstandardized Beta	Beta		
Near angle of deviation	GD: −0.054	GD: −0.639	GD: <0.001	GD: 1.000
	GU: −0.045	GU: −0.337	GU: 0.007	GU: 1.713
Base in motor fusion break amplitude	GU: 0.037	GU: 0.283	GU: 0.021	GU: 1.713
Age	GU: 0.184	GU: 0.192	GU: 0.041	GU: 1.005

We found no significant difference in PVD severity between microtropes with overlaid manifest strabismus (i.e., microtropia without identity, $n = 20$, 11 with significant distortion) and those without (microtropia with identity, $n = 20$, 8 with significant distortion; GD $Z = -0.676$, $P = 0.512$; GU $Z = -0.947$, $P = 0.355$). Thus, heterotropia does not necessarily lead to the development of PVDs, also supported by presence of significant PVDs in 5 of 13 anisometropic amblyopes who had normal binocular function and no strabismus. Sireteanu et al.[6] and others[5,22] have also identified PVDs existing in anisometropic amblyopes.

Overall, PVDs appear to have the capacity to exist in any of the three amblyopia types studied, although strabismic amblyopes appear to experience them more severely.

Is There a Relationship Between Strength of Binocular Function and Severity of PVDs?

Only 8 of 29 strabismic amblyopes had any measurable binocular function; in four participants binocular function was limited to simultaneous perception/sensory fusion with abnormal retinal correspondence. This group experienced the most severe distortions, in comparison to microtropic and anisometropic amblyopes, all of whom had some level of binocularity (Fig. 3). The primary clinical metrics that differentiated between amblyopes with and without PVDs were motor fusion, stereoacuity, and the near angle of strabismus (Tables 3, 8). These factors were strongly correlated with GD/GU indices, as well as with each other (Table 6). These findings strongly suggested a role for reduced binocular function and the near angle of deviation in the severity of PVDs, and the multiple regression analysis helped to establish the contributions made by these variables to the degree of PVD experienced (Table 7), which would not have been possible on the basis of the nonparametric analysis alone, due to the correlated nature of these variables.

Findings indicate that amblyopes with a larger angle of deviation (and subsequently poorer binocular function) had more severe distortions, in agreement with the hypotheses made in the Introduction. However, the multiple regression analysis also indicated that there was a significant contribution made by decreased base in fusional break amplitudes to severity of GU, after angle of deviation and age had been accounted for. Such a role for fusional amplitudes in GU severity, particularly base in amplitudes as the majority of our sample were esophoric/tropic ($n = 59$), would suggest that decreased binocular function can contribute to a loss of stability of the visual percept, leading to difficulties in consistently localizing stimulus position under dichoptic viewing conditions. No other research has attempted to directly correlate strength of binocular function to PVD severity before. However, findings indicate some dissociation between the impact of binocular function strength and the near angle of deviation size upon PVD severity, as demonstrated by the relatively low adjusted R^2 value in multiple regression for GD (0.401) and GU (0.329), and the strength of the reported correlations (Table 5).

While individuals with a smaller angle of strabismus and better binocular function may be less likely to develop PVDs, they can occur in individuals without strabismus and with normal binocular function, exemplified by the anisometropic amblyopes. There were also cases of strabismic amblyopes with an angle of deviation exceeding 10Δ who did not have significant PVDs ($n = 4$). Therefore, strength of binocular function and the near angle of deviation is not guaranteed to predict whether or not an individual will develop PVDs, although they appear to play a role, based on our findings.

One possibility to consider is that clinical testing of binocular single vision does not completely describe the extent of binocular function in amblyopia. It been demonstrated that the extent of suppression of the strabismic eye depends on the method used to measure it,[23] and a recent review by Hess et al.[24] discusses ways in which researchers have manipulated interocular contrast and luminance to facilitate binocular interaction between the amblyopic and fellow eye. Thus, conventional clinical testing only describes binocular potential under standard viewing conditions. With the advent of new tests of binocular combination that could be used in a clinical setting,[25,26] an area for further research could be to look at the relationship between severity of PVDs and the required parameters for successful binocular combination using such tests. It is possible that such a relationship, if one exists, could explain why some anisometropic amblyopes have binocular function within normal limits, yet still have significant PVDs. Another possibility is that the cortical disruption that occurs in amblyopia[5,22,27–29] may also affect the pattern of PVDs identified in this sample.

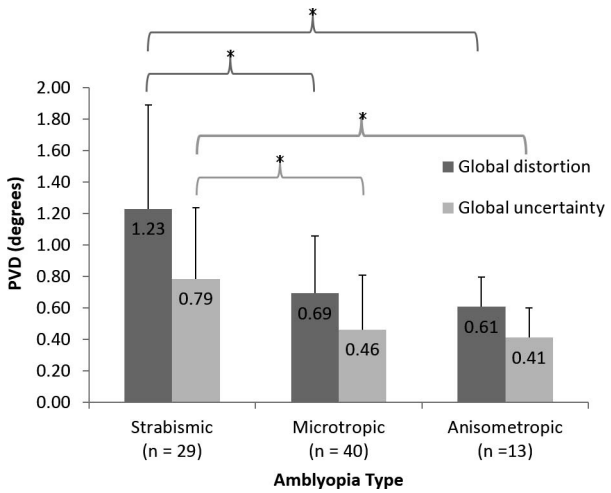

FIGURE 3. Effect of amblyopia type upon median GD and GU indices. *Error bars*: interquartile range (IQR). *Difference between amblyopia types is statistically significant.

Table 8. Clinical Parameters of Amblyopes With and Without PVDs Who Have Completed Treatment

Clinical Parameter	Amblyopes With Significant PVDs ($n = 30$)	Amblyopes Without Significant PVDs ($n = 22$)
Age at diagnosis, y; mean ± SD	3.19 ± 1.08	3.79 ± 1.52
Current VA, logMAR; mean ± SD		
Amblyopic eye	0.33 ± 0.25	0.21 ± 0.12
Fellow eye	0.07 ± 0.09*	0.02 ± 0.07
Current MSE prescription, DS; mean ± SD		
Amblyopic eye	+4.89 ± 2.23	+4.44 ± 3.11
Fellow eye	+3.93 ± 2.25	+3.46 ± 2.19
Refractive adaptation, mo; mean ± SD	10.62 ± 7.03	8.96 ± 9.05
Treatment duration, mo; mean ± SD	13.97 ± 8.90	11.61 ± 6.46
Occlusion dosage, h; mean ± SD	4.23 ± 1.07	4.21 ± 1.24
Pretreatment IOAD, logMAR; mean ± SD	0.44 ± 0.25	0.38 ± 0.24
Posttreatment IOAD, logMAR; mean ± SD	0.25 ± 0.26	0.20 ± 0.12
Number of lines improvement, logMAR; mean ± SD	0.23 ± 0.19	0.26 ± 0.19
Horizontal prism fusion range (Δ), median (IQR)		
Base in	0 (12.00)*	15.00 (13.00)
Base out	0 (25)*	32.50 (27.50)
Stereoacuity (" arc) median (IQR)	Unmeasurable (59)*	85 (6)
Near angle of deviation (Δ) median (IQR)	15.00 (14.50)*	6.00 (10.25)

Participants with no measurable stereopsis were assigned a log arc second value of 4.00.
* Significantly different to amblyopes without PVD (Mann-Whitney U test, $P < 0.05$).

Contribution of Other Clinical Parameters to PVDs

Between amblyopes with and without significant PVDs, age at diagnosis and VA in the fellow eye were significantly different (Table 4). However, these findings must be interpreted with caution—post hoc analysis revealed that the difference in age at diagnosis between amblyopes with and without significant PVDs originated from the strabismic amblyopes in the sample. When we repeated the analysis with the strabismic amblyopes excluded ($n = 53$), the difference in age at diagnosis was no longer statistically significant. This finding may therefore be artefactual because strabismic amblyopes had some of the most severe PVDs—children with strabismus tend to have their deviation noticed at a younger age and therefore diagnosis occurs earlier.

With regard to fellow eye VA, the mean difference between the two groups is approximately two letters, as listed in Table 4. Although this is statistically significant due to the consistency of its occurrence, the clinical significance of this difference is limited. While the possibility cannot be ruled out that poorer VA in the fellow eye is a potential associated with severity of PVDs, Figure 4 shows that the relationship between GD and fellow eye VA is not particularly linear, with a 6/6 (0.00 logMAR) VA being associated with GD ranging from 0.23° to 2.25°.

We found no correlation between PVDs and clinical parameters such as refractive error, amblyopic eye VA, initial amblyopia density (pretreatment IOAD) and current amblyopia density (current IOAD). These parameters are similar between amblyopes with and without PVD and were not statistically significant (Table 4). This corroborates the lack of relationship between PVDs and the primary VA deficit in amblyopia found in other studies.[3,5,6,13,21,30] This primary VA deficit is the key focus of conventional amblyopia treatment modalities, which deprive binocular vision. The existence of PVDs may be important to consider for other treatment modalities that promote binocular vision, given the relationships identified in this paper between PVD severity and strength of binocular function. An evaluation of perceptual visual distortions alongside improvements in binocular single vision during amblyopia treatment is an area for future research.

Impact of PVDs on Amblyopia Treatment Outcomes

No significant differences in treatment outcome variables (posttreatment IOAD, treatment duration, occlusion dosage) were identified between amblyopes with and without significant PVDs who had completed amblyopia treatment. There was no evidence to suggest that there was any kind of

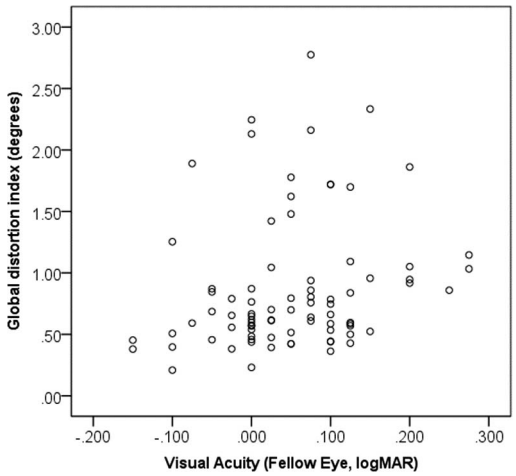

Figure 4. The relationship between GD index and fellow eye VA for individual children with amblyopia ($n = 82$). Although a positive statistically significant correlation existed (GD rho = 0.300, $P = 0.006$; GU rho = 0.267, $I = 0.015$), there is a spectrum of GD indices for any given fellow eye VA, showing the relationship is not particularly linear.

relationship between PVDs and amblyopia treatment outcomes, despite having a reasonable sample size ($n = 52$) with a range of starting IOADs (0.125–1.150 logMAR).

Of treated amblyopes, 57.6% still had significant PVDs, despite one-half of those individuals having a posttreatment IOAD less than or equal to 0.200 logMAR. Other studies have also identified the existence of PVDs in treated amblyopes.[5–14] A previous study by Fronius et al.[4,15] found GD to improve with amblyopia treatment. The current study was cross-sectional, and therefore no inferences can be made about changes in PVDs with amblyopia treatment, although our findings indicate conventional treatment protocols do not eliminate them in more than one-half of all cases.

Suggestions for the Neural Substrate of PVDs in Amblyopia

There was a lack of correlation of PVDs to the visual acuity deficit in the sample, which supports the possibility that PVDs in amblyopia may be a static factor independent of the primary amblyopic deficit in VA and contrast sensitivity. The nonlinear relationships of binocular functions, near angle of deviation and fellow eye VA with PVD severity suggests these parameters are only partly contributing to the amblyopic percept. Previously,[1] we demonstrated a prominent retinotopic component to the distortions measured. Defective binocular function and/or a large angle of deviation could potentially facilitate more extensive disruption to the cortical retinotopic map, an area for future exploration.

Conclusions

Our research has identified significant associations between binocular functions, the size of the near angle of deviation, and the severity of PVDs in children with amblyopia. In a large sample of children with amblyopia, it was demonstrated that PVDs exist at a point prevalence rate of 56.1%, are not significantly correlated with the primary VA deficit but are correlated with strength of binocular function and the near angle of deviation, and do not significantly affect the success or failure of amblyopia treatment. However, given that successful amblyopia treatment is defined exclusively in terms of acuity, these results suggest that 'treated' amblyopes may have significant residual visual impairment. The current study adds to the body of evidence highlighting the role of decorrelated binocular single vision in many aspects of amblyopia, and emphasizes the importance of restoring and improving binocular single vision in amblyopic individuals.

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